**Amendments to the Specification:**

Please replace the existing Title with the following:

~~--USE OF MONOCLONAL ANTIBODIES THAT DEFINE UNIQUE MENINGOCOCCAL B EPITOPES IN THE PREPARATION OF VACCINE COMPOSITIONS~~ METHODS FOR ISOLATING MOLECULAR MIMETICS OF UNIQUE *NEISSERIA MENINGITIDIS* SEROGROUP B EPITOPES--

Please replace the paragraph beginning on page 1, line 11 with the following amended paragraph:

-- This application is a divisional of U.S. Patent Application Serial No. 09/910,552, filed July 23, 2001, which is a divisional of U.S. Patent Application Serial No. 09/494,822, filed January 31, 2000, which is a continuation of U.S. Patent Application Serial No. 08/925,002, filed August 27, 1997, now U.S. Patent No. 6,048,257, from which applications priority is claimed pursuant to 35 U.S.C. §120; and is related to provisional patent application serial no. 60/025,799, filed August 27, 1996, from which application priority is claimed under 35 U.S.C. §119(e)(1) and which ~~is~~ applications are incorporated herein by reference in ~~its entirety~~ their entireties.--

Please replace the paragraph beginning on page 36, line 3, with the following rewritten paragraph:

-- Adjuvants may also be used to enhance the effectiveness of the vaccines. Adjuvants can be added directly to the vaccine compositions or can be administered separately, either concurrently with or shortly after, vaccine administration. Such adjuvants include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc.; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (International Publication No. WO 90/14837), containing 5% Squalene, 0.5% ~~Tween 80~~ TWEEN 80 (polyoxyethylenesorbitan monooleate), and 0.5% ~~Span 85~~ SPAN 85 (sorbitan trioleate) (optionally containing various amounts of MTP-

PE (see below), although not required) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalane, 0.4% ~~Tween 80~~ TWEEN 80 (polyoxyethylenesorbitan monooleate), 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) RibiJ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% ~~Tween 80~~ TWEEN 80 (polyoxyethylenesorbitan monooleate), and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxJ); (3) saponin adjuvants, such as StimulonJ (Cambridge Bioscience, Worcester, MA) may be used or particle generated therefrom such as ISCOMs (immunostimulating complexes); (4) Freund's Complete Adjuvant (FCA) and Freund's Incomplete Adjuvant (FICA); (5) cytokines, such as interleukins (IL-1, IL-2, etc.), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition.--

Please replace the paragraph beginning on page 42, line 18, with the following rewritten paragraph:

For preparation of the conjugate vaccine, the NPr-MenB polysaccharide was partially hydrolyzed in 10 mM sodium acetate at pH 5.5 at 50EC for 2 hours. The resulting mixture of oligosaccharides was fractionated on ~~Q-Sepharose~~ Q-SEPHAROSE (a quaternary ammonium strong anion exchanger). Oligosaccharides having an average degree of polymerization (Dp) of 2-6 were first eluted with 100 mM NaCl and discarded. Intermediate-sized oligosaccharides were eluted with 500 mM NaCl. It was subsequently determined by analytical ion exchange chromatography using a ~~Mono Q~~ MONO Q column (a quaternary ammonium strong anion exchanger) that the intermediate-sized oligosaccharides ranged in size from Dp 13 to 20 (Mean = Dp 13).

Please replace the paragraph beginning on page 42, line 30, with the following rewritten paragraph:

A terminal aldehyde group was generated at the non-reducing end of the intermediate-sized oligosaccharides by reacting them with 100 mM sodium periodate for 15-30 minutes at ambient temperature in the dark. Excess ethylene glycol was used to quench the oxidative reaction and the product was desalted on a ~~Sephadex G-25~~ SEPHADEX G-25 column (a dextran-based column). The oligosaccharide-protein conjugate was prepared by stirring a mixture of terminal aldehyde containing NPr MenB oligosaccharide with tetanus toxoid (molar ratio of 200:1, respectively) in 0.75 M potassium phosphate buffer, pH 9.0 with 40 mg/ml of sodium cyanoborohydride for one day at 40EC and two days at ambient temperature. The resultant NPr-MenB oligosaccharide-tetanus toxoid conjugate (CONJ-2) was finally purified by gel permeation chromatography on ~~Sephadex G-100~~ SEPHADEX G-100 (a dextran-based matrix) using 50 mM sodium phosphate, pH 7.0, 150 mM sodium chloride as the eluting buffer. Sialic acid and protein compositions of the conjugate vaccine were measured by the Svennerholm resorcinol reaction (Svennerholm, L. (1957) *Biochim. Biophys. Acta.* 24:604) and Lowry assays, respectively. On a weight basis, the final saccharide-to-protein ratio of the CONJ-2 conjugates ranged from 0.10 to 0.25.

Please replace the paragraph beginning on page 43, line 21, with the following rewritten paragraph:

The CONJ-2 glycoconjugate was characterized as follows. In order to demonstrate covalence (e.g., establishing a covalent linkage between the NPr-MenB OS and the protein carrier), a number of physico-chemical techniques can be used, including: SDS-PAGE; Western Blot; ~~Sephadex G-100~~ SEPHADEX G-100 gel filtration; or the like. For the purposes of the present study, SDS-PAGE was used to establish covalent attachment of the NPR-MenB OS/TT CONJ-2 glycoconjugates by revealing a shift to higher molecular weight for the conjugate band as compared to the carrier protein band, *per se*. Western blot analysis of the CONJ-2 glycoconjugates demonstrated covalence by the coincidence of positive immunoreactive signals for TT and NPr-MenB PS with specific anti-TT and anti-NPr-MenB PS antisera.

Please replace the paragraph beginning on page 44, line 17, with the following rewritten paragraph:

In addition, constructing the CONJ-2 glycoconjugates to have substantially homogenous-sized saccharide moieties of a well-defined intermediate chain length (e.g., average Dp of 10-20) is expected to result in glycoconjugates which display more consistent immunological behavior. Further, the selective end-activation (e.g., selective introduction of the aldehyde group at the non-reducing terminus) of the ~~Q-Sepharose~~ Q-SEPHAROSE chromatography-purified NPr-MenB oligosaccharides avoids the possibility of cross-linked, heterogenous structures which could arise from the use of NPr-MenB PS molecules with "active" aldehyde groups introduced at both termini. In this regard, it is likely that bi-terminally activated PS (having aldehyde groups at both ends) could be derived from a periodate oxidation of N-acylated MenB PS previously exposed to $NaBH_4$ during the N-deacetylation procedure.

Please replace the paragraph beginning on page 47, line 25, with the following rewritten paragraph:

The concentrations of unpurified monoclonal antibodies were determined using an ELISA capture assay and a radial immunodiffusion assay. Particularly, a capture ELISA procedure was used to determine the concentration of each of the anti-NPr-MenB PS monoclonal antibodies. Microtiter plates (~~Immulon 2~~ IMMULON 2, available from Dynatech Laboratories, Inc.) containing 100 µl/well of affinity purified rabbit anti-murine IgG, IgM and IgA (H and L, Zymed) diluted to 1 µg/ml in 10 mM PBS (pH 7.4) were incubated overnight at 4EC. After washing three times with PBS, the wells were filled with 250 µl of Blocking Buffer (PBS containing 1% bovine serum albumin (BSA) and 0.1% sodium azide, pH 7.4) and incubated for 30 to 60 minutes at ambient temperature to block nonspecific binding sites. The plates were washed three times with Washing Buffer (PBS containing 0.1% ~~Tween 20~~ TWEEN 20 (polyoxyethylenesorbitan monolaurate) and 0.1% sodium azide, pH 7.4). Antibodies to be tested were diluted in Diluting Buffer (PBS containing 1% BSA, 0.1% ~~Tween 20~~ TWEEN 20 (polyoxyethylenesorbitan monolaurate) and 0.1% sodium azide, pH 7.4) and then added at 100 µl

per each well. The plates were covered and incubated overnight at 4EC. Murine IgG1, IgG2b, IgG3 and IgM immunoglobulin standards (available from Southern Biotechnology Associates), at concentrations ranging from 500 ng/ml to 4 ng/ml, were used to construct standard curves for quantifying antibody concentrations.

Please replace the paragraph beginning on page 55, line 3, with the following rewritten paragraph:

A solid phase ELISA procedure was used to assess the concentration dependent binding of the antibody molecules to NPr-MenB PS in the presence of buffer alone or 25 μg/ml of a soluble NPr-MenB PS inhibitor. Biotinylated NPr-MenB PS-ADH was prepared using the method of Sutton et al. (1985) *J. Immunol. Methods* 82:215. Microtiter plates (~~Immulon 2~~ IMMULON 2, available from Dynatech Laboratories, Inc.) containing 100 μl/well of avidin (4 μg/ml Extr Avidin, Sigma) in 10 mM PBS (pH 7.4) were incubated overnight at 4EC. After washing three times with PBS, 100 μl of biotinylated NPr-MenB PS in PBS was added to each well and incubated at 37EC for 2 hours. The plates were washed three times with PBS, and the wells were filled with 250 μl of Blocking Buffer and incubated for 30 to 60 minutes at ambient temperature to block nonspecific binding sites.

Please replace the paragraph beginning on page 69, line 4, with the following rewritten paragraph:

Bacterial Challenge: One to two hours after the initial injection, the infant rats received a bacterial challenge injection intraperitoneally of $10^5$ ~~Neisseria meningitidis~~ *Neisseria meningitidis* group B bacteria of the strain IH 534 (rat passaged five times) in a final volume of 100 μl. Six hours after bacterial inoculation, bacteremia and meningitis development was assessed by culturing blood and cerebrospinal samples taken from the infant rats.

Please replace the paragraph beginning on page 72, line 1, with the following rewritten paragraph:

Panning of the libraries was carried out using the techniques described by Smith et al. (1993) *Methods in Enzymology* 217:228, with the exception that the antibodies were absorbed directly to microtiter plates. 100 µl solutions containing representative monoclonal antibodies (1 µg/ml of SEAM-2, SEAM-3, SEAM-5, SEAM-7, SEAM-12, SEAM-16, SEAM-18, and SEAM-28), or a corresponding concentration of control antibodies (a murine anti-MenB PS-specific monoclonal (2-1B), a human anti-Hib PS monoclonal (ED8), and a murine monoclonal of irrelevant specificity (Laz2))were incubated overnight at 4EC in microtiter plates (~~Immunolon II~~ IMMULON II). After washing the wells with PBS, Blocking Solution (5% (w/v) non-fat dry milk, 0.2% (w/v) ~~Tween 20~~ TWEEN 20 (polyoxyethylenesorbitan monolaurate), 0.02% (w/v) sodium azide in PBS) was added to completely fill the wells, and the plates were then incubated at ambient temperature for 3 hours. The blocked plates were washed six times with PBS.

Please replace the paragraph beginning on page 80, line 11, with the following rewritten paragraph:

The 10 ml suspension of outer membrane protein was retreated with 5 ml of the Detergent Solution, and then warmed to 56EC for 30 minutes. After cooling, lipopolysaccharide (LPS) was removed from the outer membrane protein by chromatography, 2 ml at a time, using a 2 cm x 20 cm ~~Sephadex G-100~~ SEPHADEX G-100 column (Pharmacia Fine Chemicals, Piscataway, N.J.) in a second detergent solution (1% DOC, 0.05 M glycine, and 0.005 M EDTA, pH 8.8). The peak fractions were collected, warmed to 30EC and sterile-filtered through a 0.2 µm membrane filter directly into 4 volumes of cold, filter-sterilized ethanol. This mixture was incubated at 4EC overnight. The resulting precipitate was collected by centrifugation at 16,000 x g for 10 minutes, and resuspended in 1 ml of sterile distilled water. The resulting OMP preparation was soluble but slightly opalescent, and was stored at -60EC.

Please replace the paragraph beginning on page 80, line 28, with the following rewritten paragraph:

Preparation of Peptide/OMP Vesicles. Vaccines were prepared from peptides Pep 5 and Pep 8, or from a mixture of peptides Pep 1 - Pep 9. To facilitate hydrophobic complexing of the

peptides to the OMP vesicle, each peptide was modified by the addition at the amino terminus of a hydrophobic tail (Lauryl-GLY-GLY) and a carboxyl amide as described above for the ELISA. For each vaccine, 5 mg of peptide was dissolved in 100 µl dimethylsulfoxide (DMSO) (SIGMA, Saint Louis, MO). The resulting solution was diluted to 750 µl in buffer containing 50 mM 4-(-2-hydroxyethyl)-1-piperazineethanesulfonic Acid (Hepes), pH 8.0, and 1 M potassium ferricyanide (SIGMA, Saint Louis, MO). 7.5 µg of zwitterionic detergent (Empigen, Calbiochem, La Jolla, CA) was then added to the above peptide solution. After incubation at room temperature for 1 hour, each of the peptide solutions was combined with 250 µl of outer membrane protein (OMP) vesicles (20 mg/ml) for a total volume of 1 ml. The solution was heated to 75EC for 20 minutes. After cooling to room temperature, the OMP/Peptide mixture was added to a ~~Slide-a-Lyzer~~ SLIDE-A-LYZER (Pierce, Rockford, IL) a dialysis cassette with a 10,000 molecular weight cut off, and dialyzed in 1 L PBS overnight. The PBS solution (1 L) was changed twice over 8 hours.

Please replace the paragraph beginning on page 84, line 13, with the following rewritten paragraph:

Deposits of biologically pure cultures of the following hybridoma cell lines were made with the American Type Culture Collection (ATCC), ~~12301 Parklawn Drive, Rockville, Maryland~~ 10801 University Boulevard, Manassas, VA 20110-2209. The accession numbers indicated were assigned after successful viability testing, and the requisite fees were paid. The deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of viable cultures for a period of thirty (30) years from the date of deposit. The organisms will be made available by the ATCC under the terms of the Budapest Treaty, and subject to an agreement between Chiron Corporation and the ATCC, which assures permanent and unrestricted availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 U.S.C. §122 and the Commissioner's rules pursuant thereto (including 37 C.F.R. §1.12 with

particular reference to 886 OG 638). Upon the granting of a patent, all restrictions on the availability to the public of the deposited cultures will be irrevocably removed.